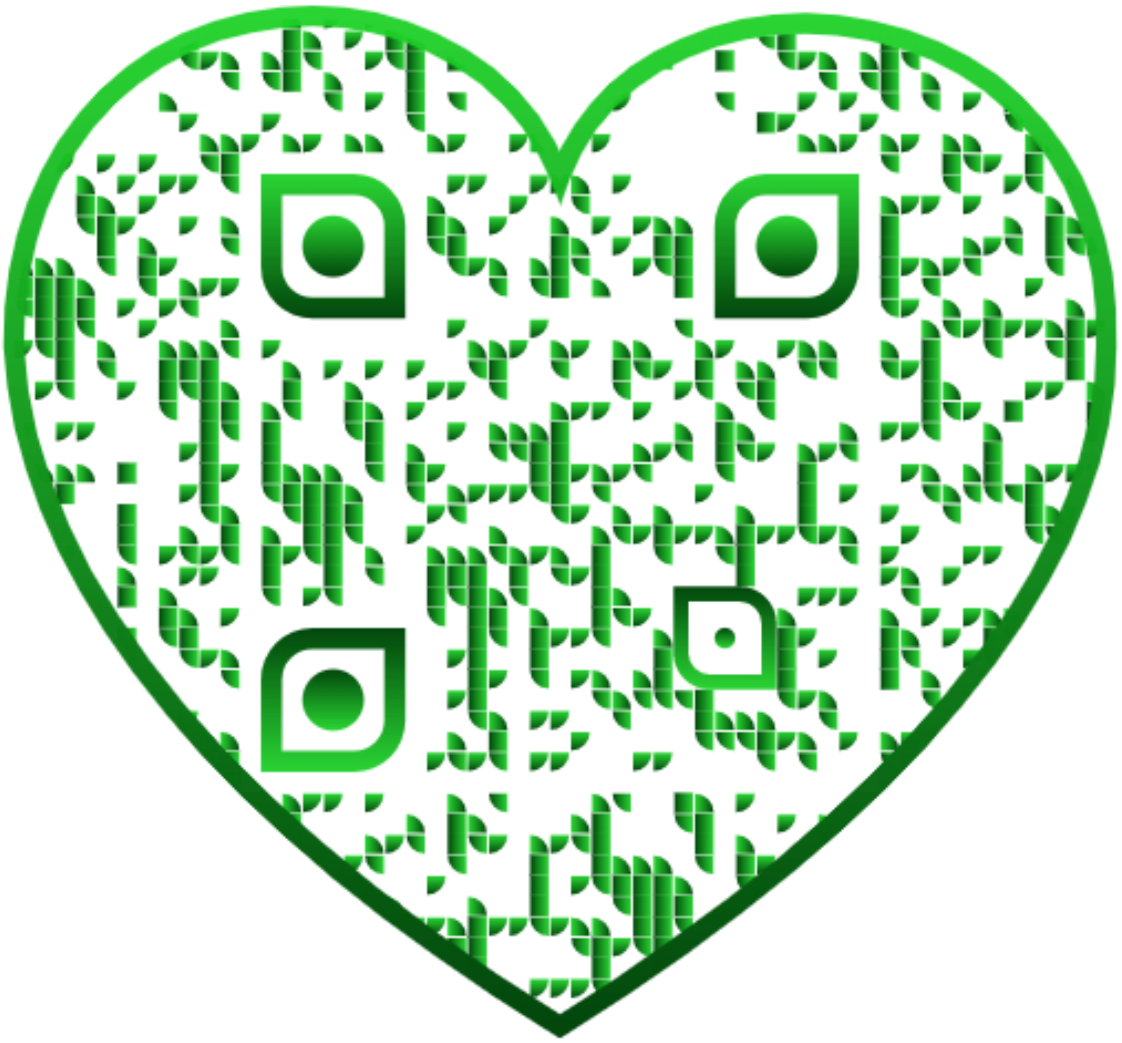
2. Factors affecting oral drug absorption

- GIT anatomy and physiology
- Physiologic factors
- Physiochemical factors
- Formulation factors



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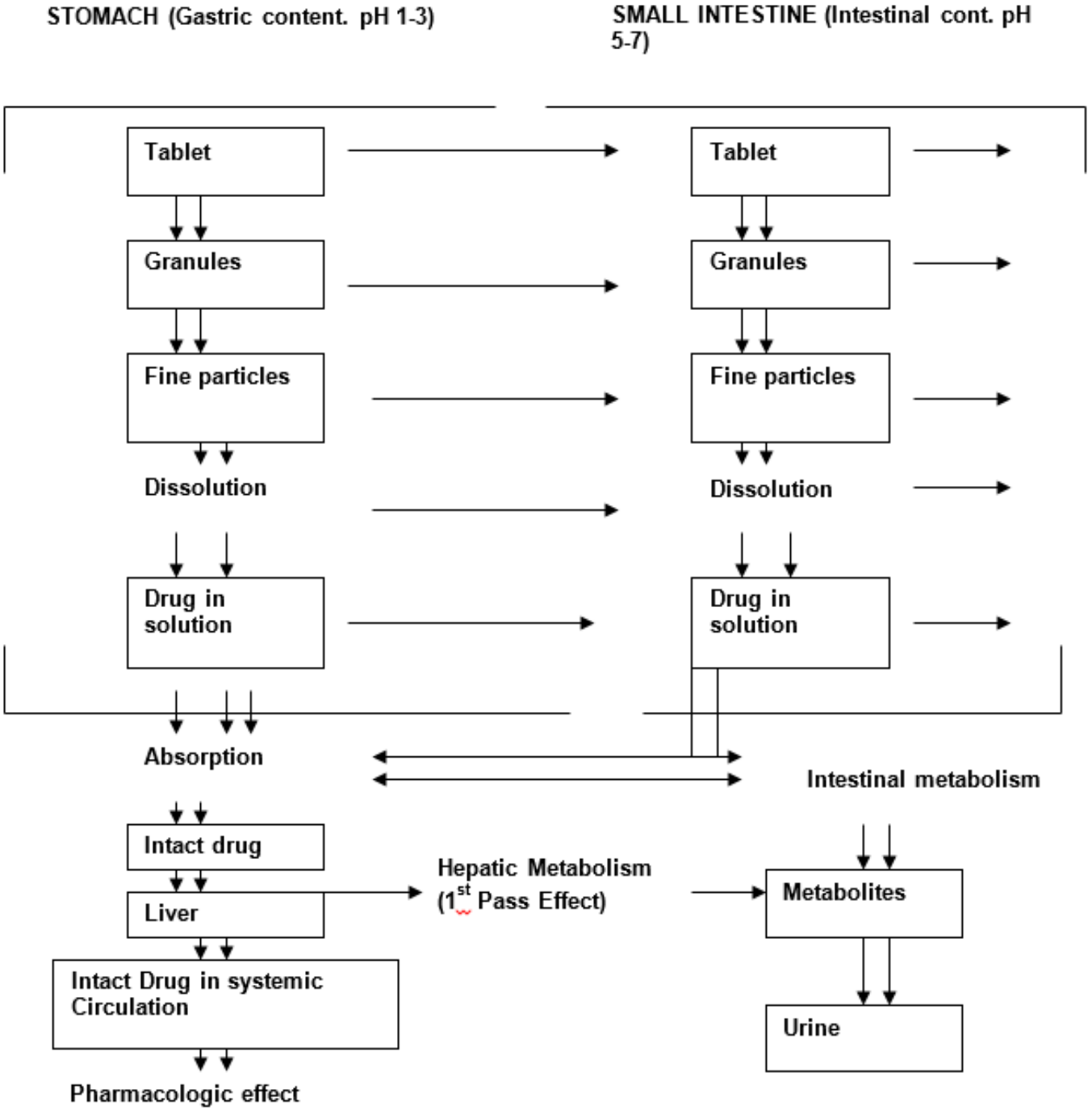
- For a drug to be effective, enough of it needs to reach its site(s) of action and stay there long enough to be able to exert its pharmacological effect.
  - This is a function of: the drug, its dosage form and the route by which it is administered.
- If a drug is given IV, it is administered directly into the blood, and it is 100 % bioavailable.
- Extravascular routes don’t guarantee that the whole dose will reach systemic circulation intact.
  - Such routes involve the absorption of the drug into the blood.


STOMACH (Gastric content. pH 1-3)
SMALL INTESTINE (Intestinal cont. pH 5-7)
Tablet
Granules
Fine particles
Dissolution
Drug in solution
Tablet
Granules
Fine particles
Dissolution
Drug in solution
Absorption
Intestinal metabolism
Intact drug
Liver
Intact Drug in systemic Circulation
Pharmacologic effect
Hepatic Metabolism
(1st Pass Effect)
Metabolites
Urine

...

- The **onset**, **intensity** and **duration** of therapeutic effect of most drugs depend on different factors

- The main factors affecting oral absorption:

    1. Physiological factors

    2. Physical-Chemical Factors

    3. Formulation (Dosage form) Factors

- These factors play important role in:
  - Bringing the drug to the biological site in the body in quantities required.
  - Sustaining it at that concentration for the desired length of time.
  - Getting the drug out of the site after it has performed the desired effect.

Physiological Factors affecting oral Absorption

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- It is important to understand the physiologic and pathologic factors affecting drug absorption for proper drug product selection.

- The systemic availability and onset of drug action are affected, among others, by:

  - Blood flow to the administration site

  - The physicochemical characteristics of the drug and the drug product

  - Any pathophysiologic condition at the absorption site.

GI Physiology

- The major segments of the GIT differ from one another
  - Anatomically and morphologically
  - With respect to secretions and pH
- The normal physiologic processes of the GIT may be affected by diet, contents of the GIT, hormones, the visceral nervous system, disease, and drugs.

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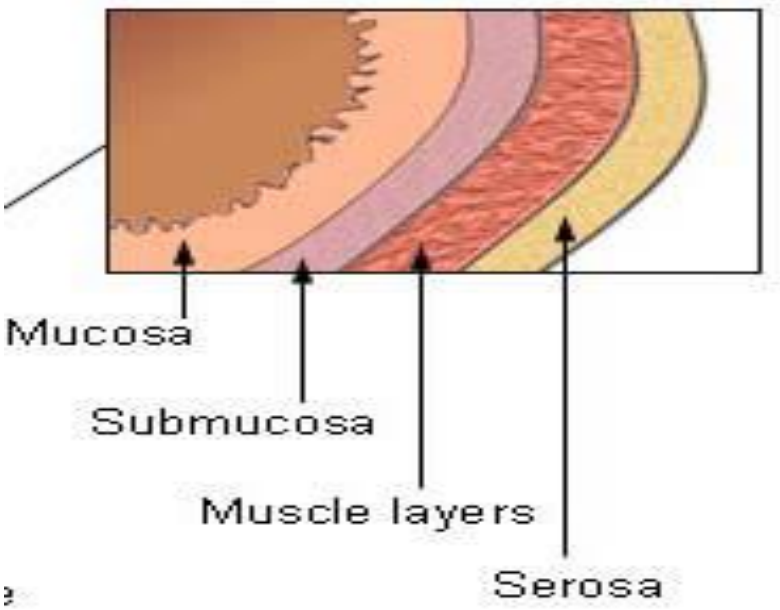
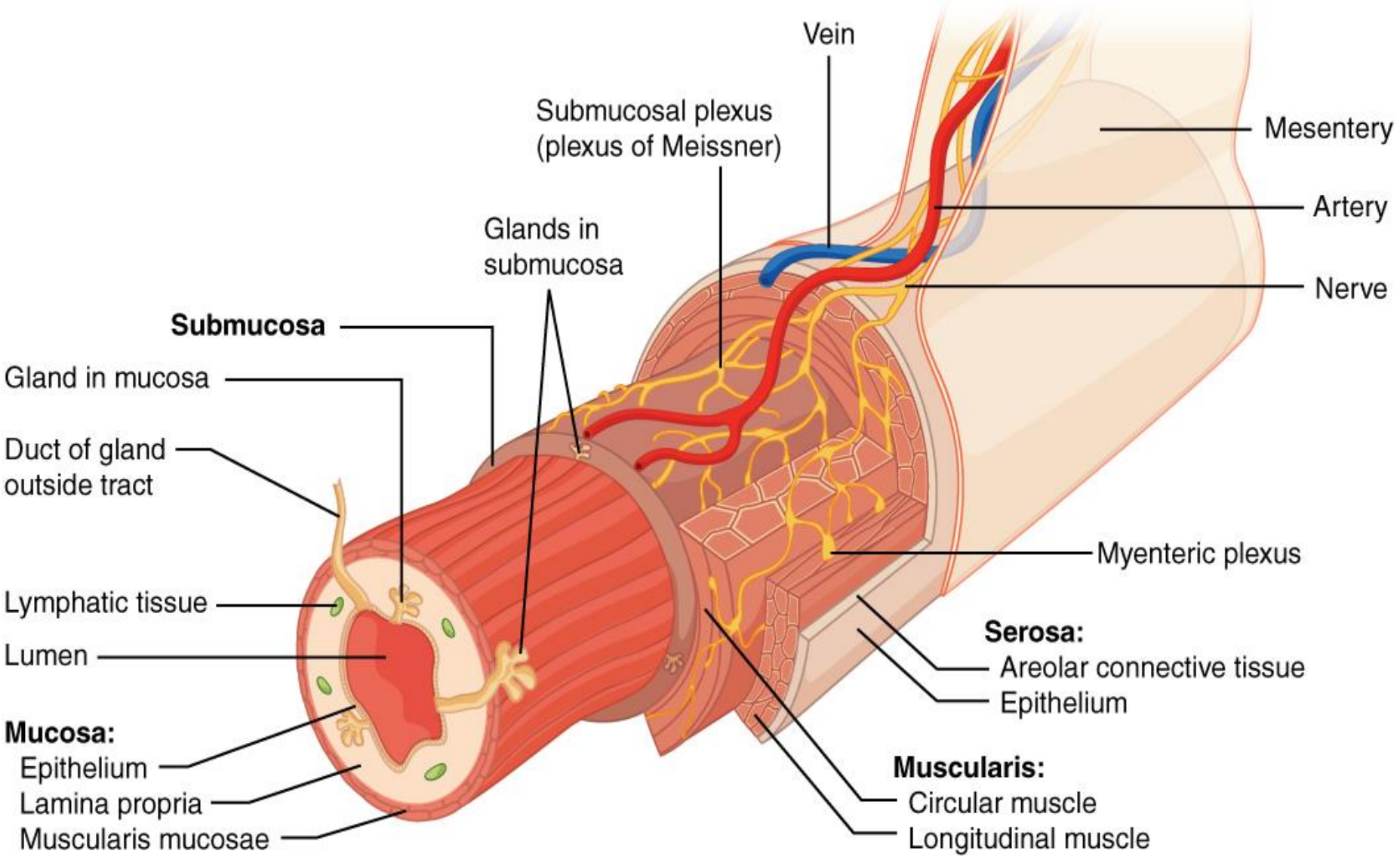
The GIT wall

- Consists four principal histological layers:




Vein
Submucosal plexus
(plexus of Meissner)
Mesentery
Artery
Glands in
submucosa
Nerve
Submucosa
Gland in mucosa
Duct of gland
outside tract
Myenteric plexus
Lymphatic tissue
Lumen
Serosa:
Areolar connective tissue
Epithelium
Mucosa:
Epithelium
Lamina propria
Muscularis mucosae
Muscularis:
Circular muscle
Longitudinal muscle

...

- **Serosa**: outer layer of epithelium, provides structural support to organs.
- **Muscularis externa**: contains two layers of smooth muscle
  - Outer longitudinal layer - shortens tract, which is important in mixing and propulsive movement of GI contents
  - Thicker inner circular layer - prevents food traveling backward

- **Sub-mucosa**: layer of connective tissue supporting mucosa and joins it to underlying smooth muscles.
  - Richly supplied with blood and lymphatic vessels, and network of nerve cells.
- **Mucosa**: composed of three layers
  - Muscularis mucosa
  - Lamina propria
  - Epithelium

- **Muscularis mucosa** – thin layer of smooth muscle
  - Alter local conformation of mucosa
  - Enhance contact between epithelium and contents of lumen
- **Lamina propria** – thin layer of connective tissue
  - Contains capillaries and lymph vessels
  - Contain glands with ducts opening to mucosal epithelium- secrete mucus

- **Epithelium** – selective absorption, secretion, protective functions
  - Its covered by layer of mucus
    - This serve as protective layer and mechanical barrier
    - Its constantly changing mix of secretions and exfoliated cells
    - Components: mucin (large glycoproteins) + water (~95%)
    - Mucus layer: 5 μm to 500 μm, with 80 μm average

Esophagus

- It serves to move boluses of food, drink or drug formulations from the buccal cavity, through the lower esophageal sphincter and into the stomach.
- Ingested materials have a very short contact time with esophageal tissue.
- It is a 25 cm long, 2 cm diameter muscular tube.

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- Lined with stratified squamous epithelium, but the lowest 2 cm or so is lined with gastric mucosa.
- The pH of the normal esophageal lumen is usually between 5 and 7.
- In upright position, transit of materials is assisted by gravity.
  - Esophageal transit of DFs is 10 - 14 s.
- Limited biopharmaceutical importance (Lodging of DFs)

Stomach

- The stomach has several functions:
  - It acts as a reservoir for food
  - It processes it into fluid chyme which facilitates the absorption of nutrients from SI
  - It regulates the delivery of food to the SI
  - It produces acid which is bacteriostatic
- Location - left upper part of the abdomen immediately below the diaphragm.

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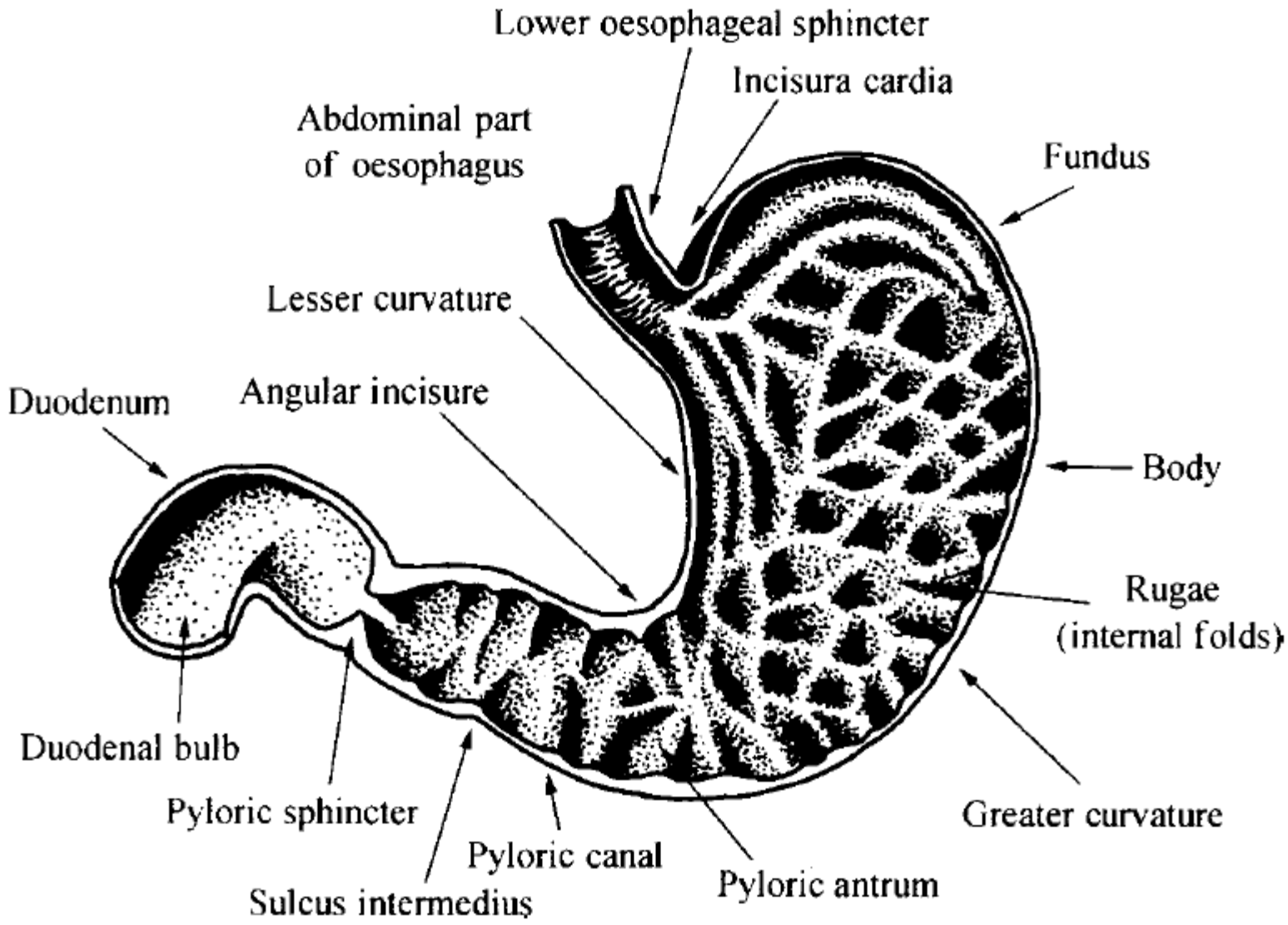
- Very little drug absorption occurs from the stomach, because of the small SA available for absorption.

- **High biopharmaceutical importance, as the gastric emptying can dictate drug absorption from SI.**

Anatomy

- Can be divided into four anatomical regions:
  - Fundus - produces slow sustained contractions
  - Body - acts as a reservoir for ingested food and liquids.
  - Antrum - mix and pump (gastric emptying)
  - Pylorus - mix and pump (gastric emptying)


Lower oesophageal sphincter
Incisura cardia
Abdominal part of oesophagus
Fundus
Lesser curvature
Angular incisure
Duodenum
Body
Rugae (internal folds)
Duodenal bulb
Pyloric sphincter
Pyloric canal
Sulcus intermedius
Pyloric antrum
Greater curvature

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- The functional regions of the stomach do not correspond to the anatomic regions.
  - Functionally, the stomach can be divided into the gastric reservoir and the gastric pump

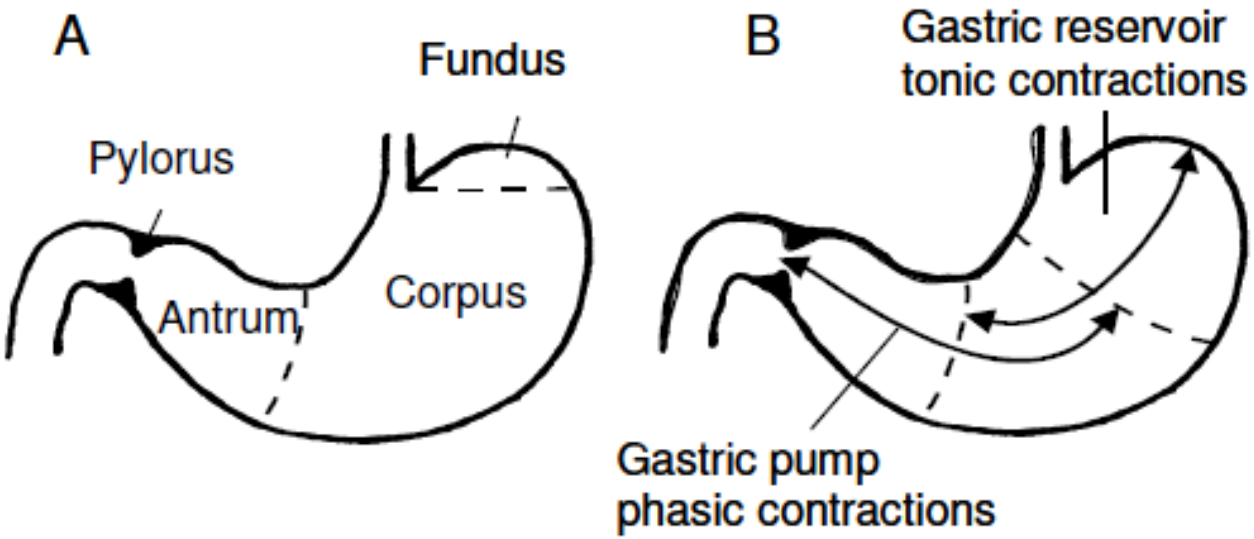

Fig. The anatomic (A) and functional (B) regions of the stomach.

Blood and nerve supply

- Arterial blood is brought to the stomach via many branches of the celiac trunk.
- Blood from the stomach is returned to the venous system via the portal vein, which carries the blood to the liver.
- Both parasympathetic and sympathetic divisions of the autonomic nervous system supply the stomach.

Gastric Motility

The fasted state

- The stomach will revert to the fasted pattern of motility in the absence of digestible food, or when it is empty.
- The fasted state is associated with various cyclic events, commonly referred to as the migrating motor complex (MMC), which regulates GI motility patterns.
- After a meal, the digestible food will have been processed to chyme and passed to the SI leaving a residue of mucus and undigested solids.

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- The undigested solids remain in the stomach until the SI has finished absorbing nutrients from the chyme.
    - Approximately 2 h after the last of the digestible food has left the stomach.
- At this point the digestive phase activity ceases and is replaced by the interdigestive phase.
    - This is normal resting condition of the stomach and small intestine.

- The MMC is organized into alternating cycles: Phases I to IV

Phase I

- A state in which the stomach and small intestine show no motor activity,
- The quiescent period, lasts from 30 to 60 min
- It is characterized by a lack of secretory, electrical, and contractile activity.

Phase II

- Exhibits intermittent action for 20–40 min during which contractile motions increase in frequency and size.
- Bile enters the duodenum during this phase.

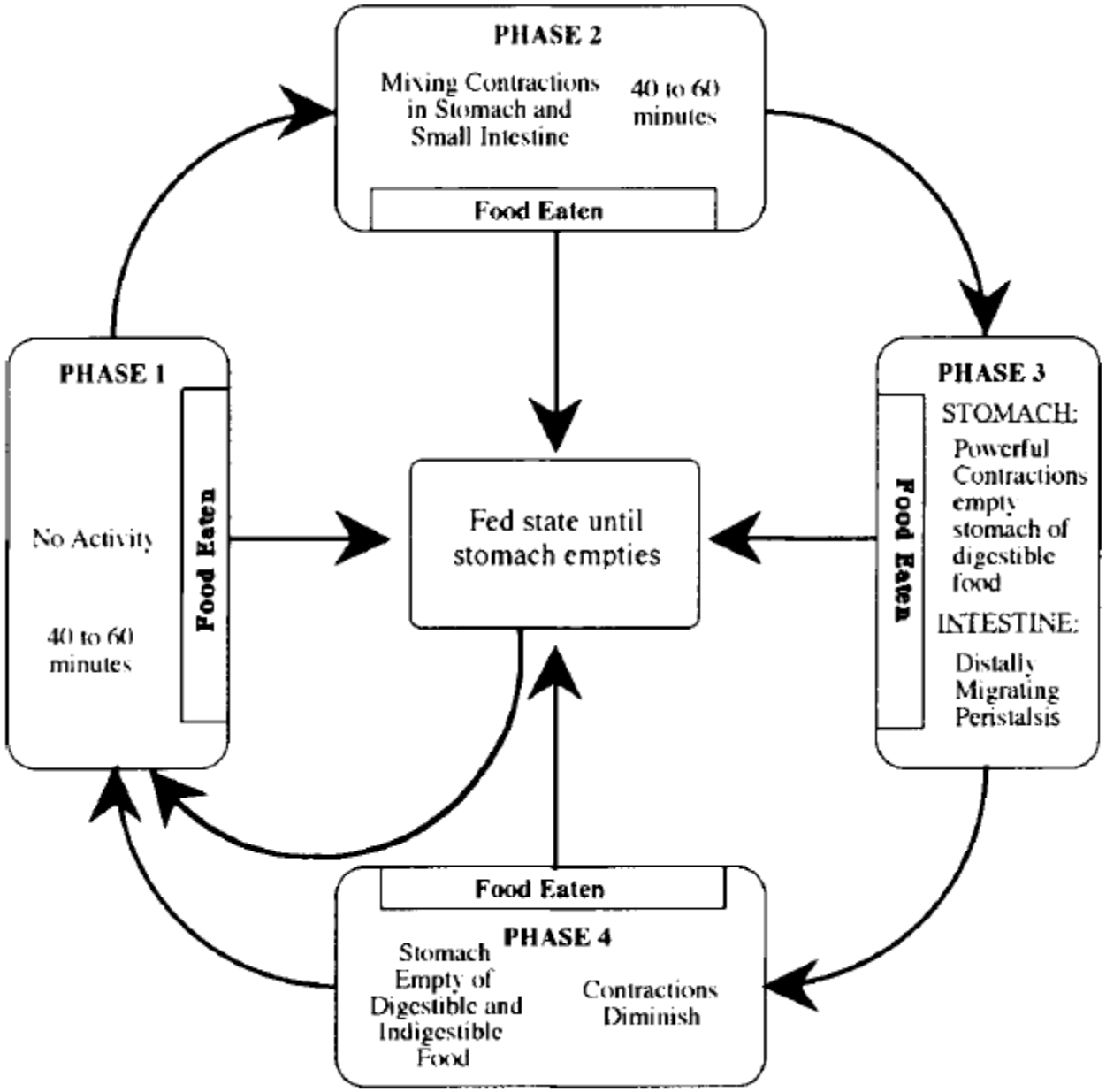
Phase III

- This is characterized by intense, large, and regular contractions, termed **housekeeper** waves, that sweep off undigested food
- It last 10 - 20 min.

Phase IV

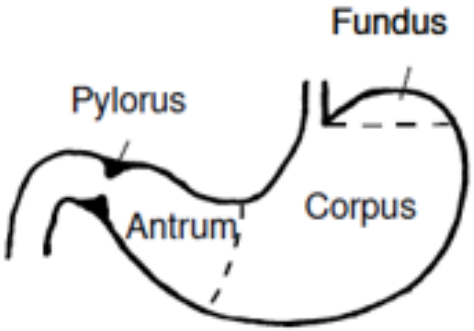
- This is the transition period of 0–5 min between Phases III and I.

The above series of electrical events originates in the foregut and continues to the terminal ileum in the fasted state, repeating every 2 - 3 hrs.


PHASE 2
Mixing Contractions in Stomach and Small Intestine
40 to 60 minutes
Food Eaten
PHASE 1
No Activity
40 to 60 minutes
Food Eaten
Fed state until stomach empties
PHASE 3
STOMACH:
Powerful Contractions empty stomach of digestible food
INTESTINE:
Distally Migrating Peristalsis
Food Eaten
Food Eaten
PHASE 4
Stomach Empty of Digestible and Indigestible Food
Contractions Diminish

The fed state

- The adult capacity of the stomach is about 1500 ml.
- The average (western) daily intake of food and drink is 3 to 4 kg
- It is estimated that another 5 liters of fluids such as saliva, gastric juice, pancreatic juice and other body liquids are added to this.



- The uppermost third of the stomach, or fundus, adapts to the varying volume of ingested food
- The stomach elicits a fed pattern of motility in response to:
  - The presence of food with calorific value
  - The presence of a large quantity of small particle size indigestible material.

- The mixing, grinding and emptying of food all occur together.

- The periodic opening of the pylorus during the fed phase of motility can explain how some large particles, including intact large fragments of tablets, can be emptied during this cycle.

- Solids and liquids do not empty from the stomach together as a homogeneous mass.
    - Liquids empty according to the pressure gradient between the stomach and duodenum.
- Larger particles require a longer period of digestion to break them down into a size suitable to exit through the pylorus.
    - Small indigestible solids of between 1 to 5 mm in diameter are progressively emptied during the whole postprandial period even before liquid emptying is completed.

- The empty stomach has a volume of approximately 50 ml which increases to over 1 liter when full.

- In general, the larger the amount of food ingested, the longer the period of fed activity.

- Gastric emptying rates correlate with the nutritive density of the meal.

- Two sets of receptors to control the delivery of the chyme to the duodenum by energy density:
  - One stimulated by the osmotic properties of the digestion products of carbohydrate and protein
  - The other stimulated by the digestion products of fat.
- Fatty foods are believed to delay gastric emptying.

- Gastric emptying follows a **circadian rhythm**, with slower emptying occurring in the afternoon compared to the morning.

- Over a 50% decrease in emptying rate in the solid phase of the meal when it was eaten in the evening compared to the morning.

- The gastric emptying of tablets, pellets and liquids is highly dependent on the presence and amount of food in the stomach.

- Large tablets can either disintegrate in the stomach and empty with the digestible phase of the meal.
    - If they are designed to remain intact will be treated as indigestible material and empty with phase III.
- Large non-disintegrating capsules will empty with phase III of the MMC.

- The length of the retention is proportional to the meal size.
    - If a large single unit is given with a heavy meal and the subject is fed at regular intervals, the unit can remain in the stomach for longer than 8 hours.
- The effect of meal size on the gastric emptying times of single units is extremely important.

• • •

- The gastric emptying rates of **multiparticulate** dosage forms are not as severely affected by the presence or absence of food as are large **single units**.

- After dosing with a capsule containing pellets during or 10 min after a meal, pellets tend to remain in the upper half of the stomach.

    - If the capsule is taken 10 minutes prior to a meal, the pellets empty faster

- Ingestion of an anti-reflux agent prior to meal causes it to empty before the food, and in addition it does not form the floating raft which is required for its action.

- The gastric residence of floating formulations can be prolonged by frequent intake of meals.

  - The buoyant raft empties faster than food in subjects lying on their left side or their backs.

  - When the subjects lay on their left side the raft was presented to the pylorus ahead of the meal and so emptied first.

- Assignment I –
  - Read on gastro-retentive systems
  - Submit max. 2 pages of your note

Small intestine

- Longest (4 - 5 m) and most convoluted part.
- Extend from pyloric sphincter to ileocaecal junction
- 2 Main functions:
    - Digestion
    - Absorption

- 3 parts:
    - Duodenum 20 - 30 cm
    - Jejunum ~ 2 m
    - Ileum ~ 3 m
- These regions are not anatomically distinct, although there are differences in absorptive capability and secretion.

- Duodenum contains duodenal digestive glands and Brunner's glands.
    - Brunner's glands produce a protective alkaline secretion which does not contain any enzymes.
- The jejunum is thicker walled and more vascular than the duodenum, and has larger and numerous villi than the ileum.
- In the ileum, the lymphatic follicles (Peyer's patches) are larger and more numerous.

Intestinal Mucosa

- The small intestine consists of the serosa, the muscularis, the submucosa and the mucosa.
- The surface area of the small intestinal mucosa is greatly increased by:
  - The folds of Kerckring
  - Villi and microvilli (brush border)
  - And is about 200 m^2

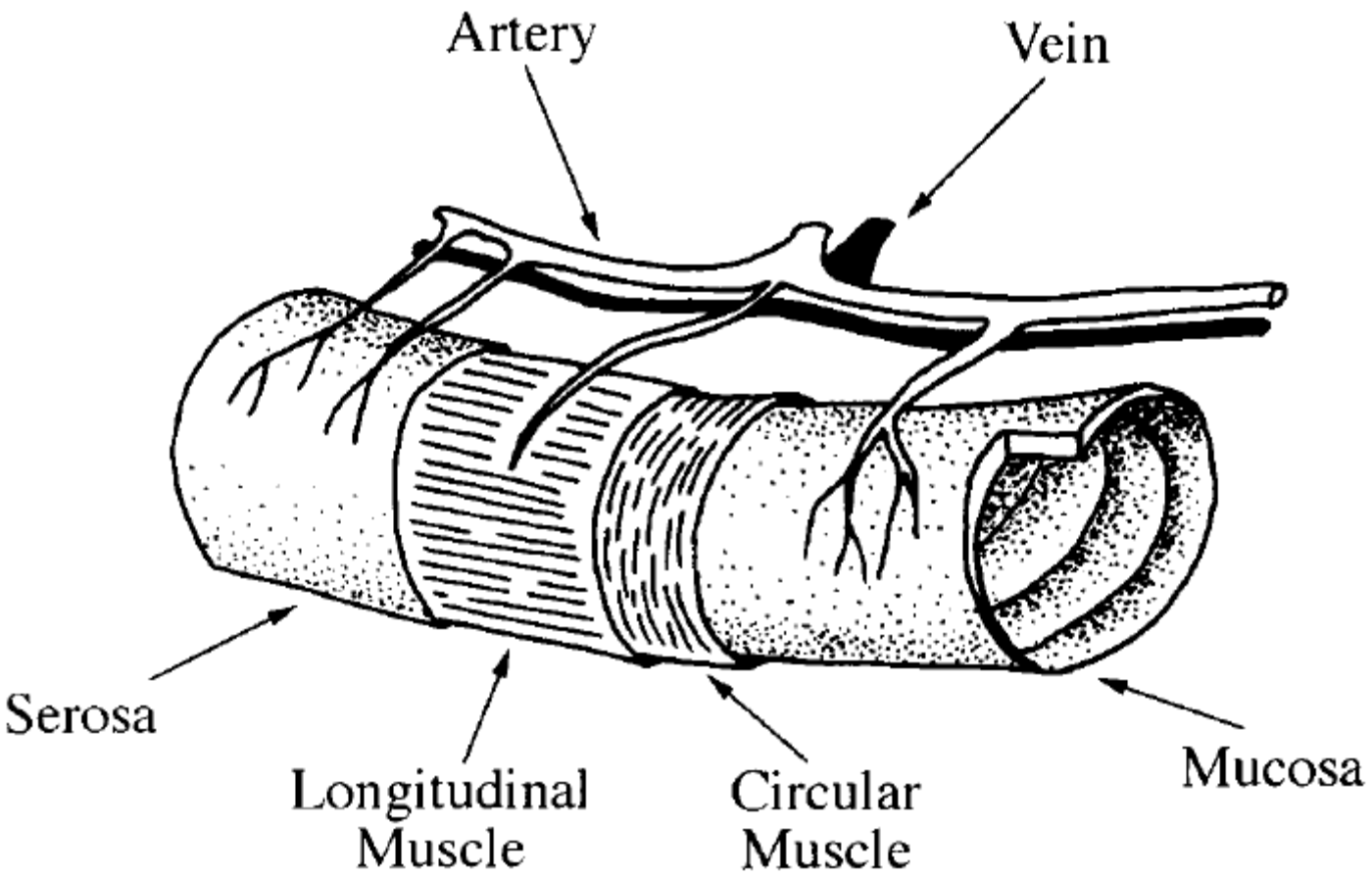
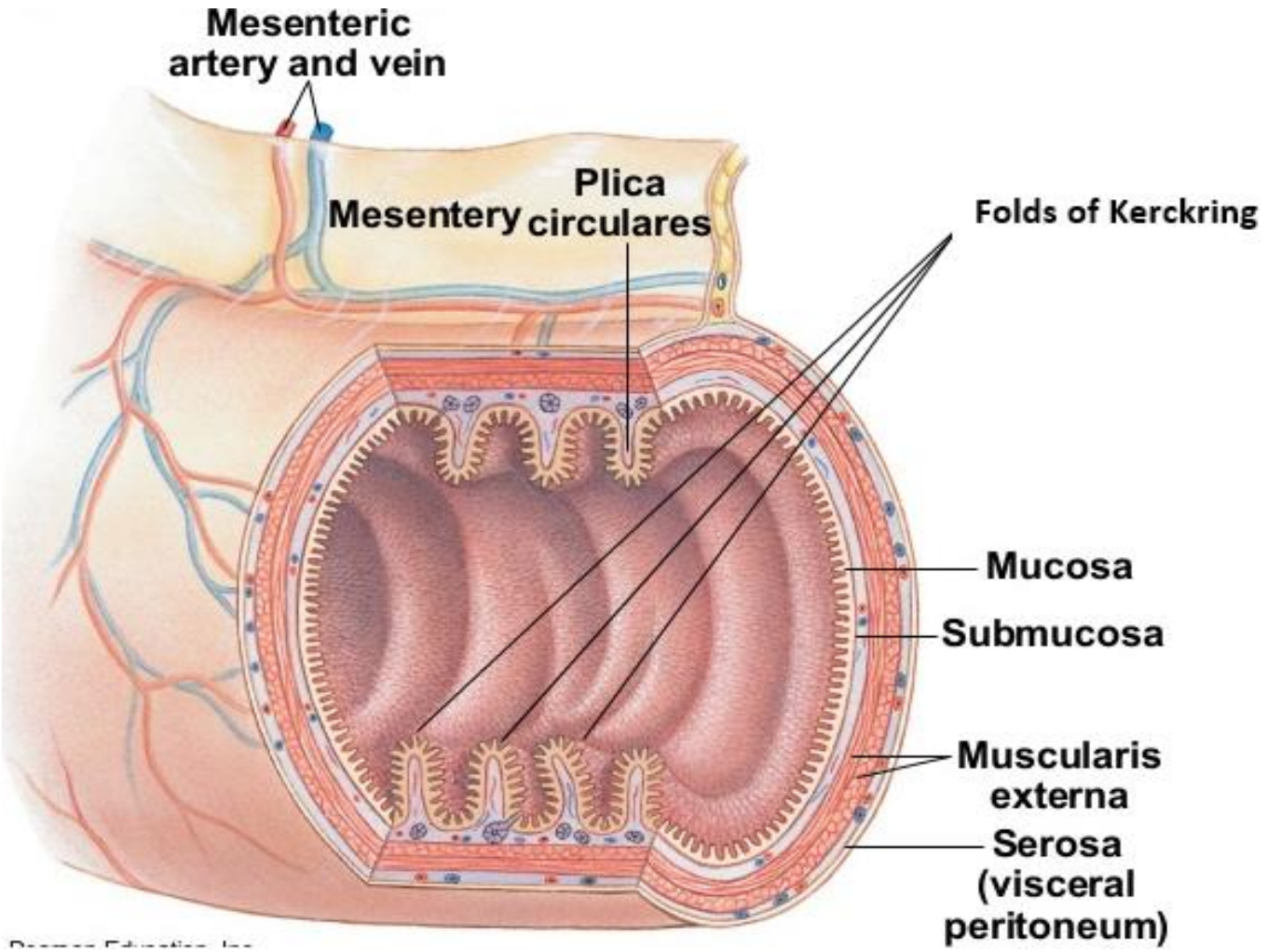


Fig. Section of the small intestine

Folds of Kerckring

- The folding of the epithelium
- The folds increase the surface area by a factor of 3.
- Well developed in the duodenum and jejunum
- They also aid mixing of the chyme in the small intestine.


Mesenteric artery and vein
Mesentery
Plica circulares
Folds of Kerckring
Mucosa
Submucosa
Muscularis externa
Serosa (visceral peritoneum)

Villi

- Are "finger-like" projections.
- About 5 million villi, each about 0.5 to 1 mm long.
- Duodenal villi are shorter and broader than those found in the jejunum.
- Each villus contains an arteriole and a venule, and also a blind-ending lymphatic vessel called a lacteal.
- The villi increase the surface area by a factor of 30.

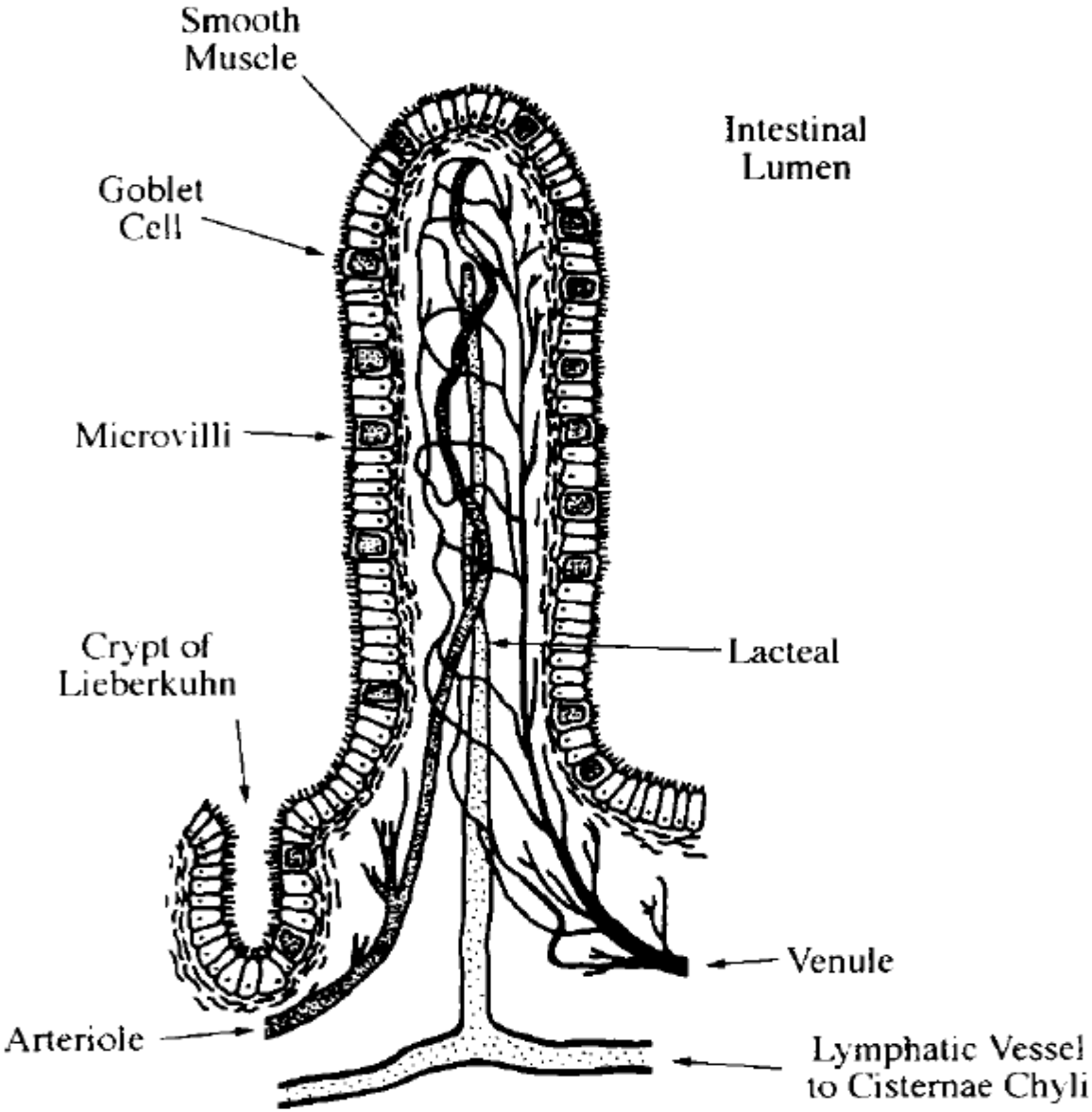


Fig. Structure of a villus.

Microvilli

- These are brush-like structures covering villi (about 1 μm long & 0.1 μm wide).
- Specific receptor proteins are located on the microvillus membrane-surface coat complex.
- The microvillus increase the surface area by a factor of 600.

- Reading assignment
  - Intestinal Epithelium.
  - Crypts of Lieberkühn (Paneth cells, goblet cells, undifferentiated cells, endocrine cells).
  - The GI circulation and the lymphatic supply.

Large intestine

- The large intestine is responsible for:
  - The conservation of water and electrolytes
  - Formation of a solid stool, and
  - Storage of feces until a convenient time for defecation.

- It extends from the ileo-caecal junction to the anus and is approximately 125 cm long.
    - Caecum (~ 8.5 cm)
    - Ascending colon (~ 20 cm)
    - Transverse colon (> 45 cm)
    - Descending colon (~ 30 cm)
    - Sigmoid colon (~ 40 cm)
    - Rectum (~ 12 cm)

- No specialized villi but microvilli on absorptive epithelial cells of the colon.

- Permanently colonized by extensive number and variety of **bacteria**, which are capable of several metabolic reactions.

  - Recent interest to exploit **enzymes** produced by these bacteria to <u>targeted drug delivery</u> to this region.

- Some biopharmaceutical importance: Targeted drugs to colon (**prodrug**)

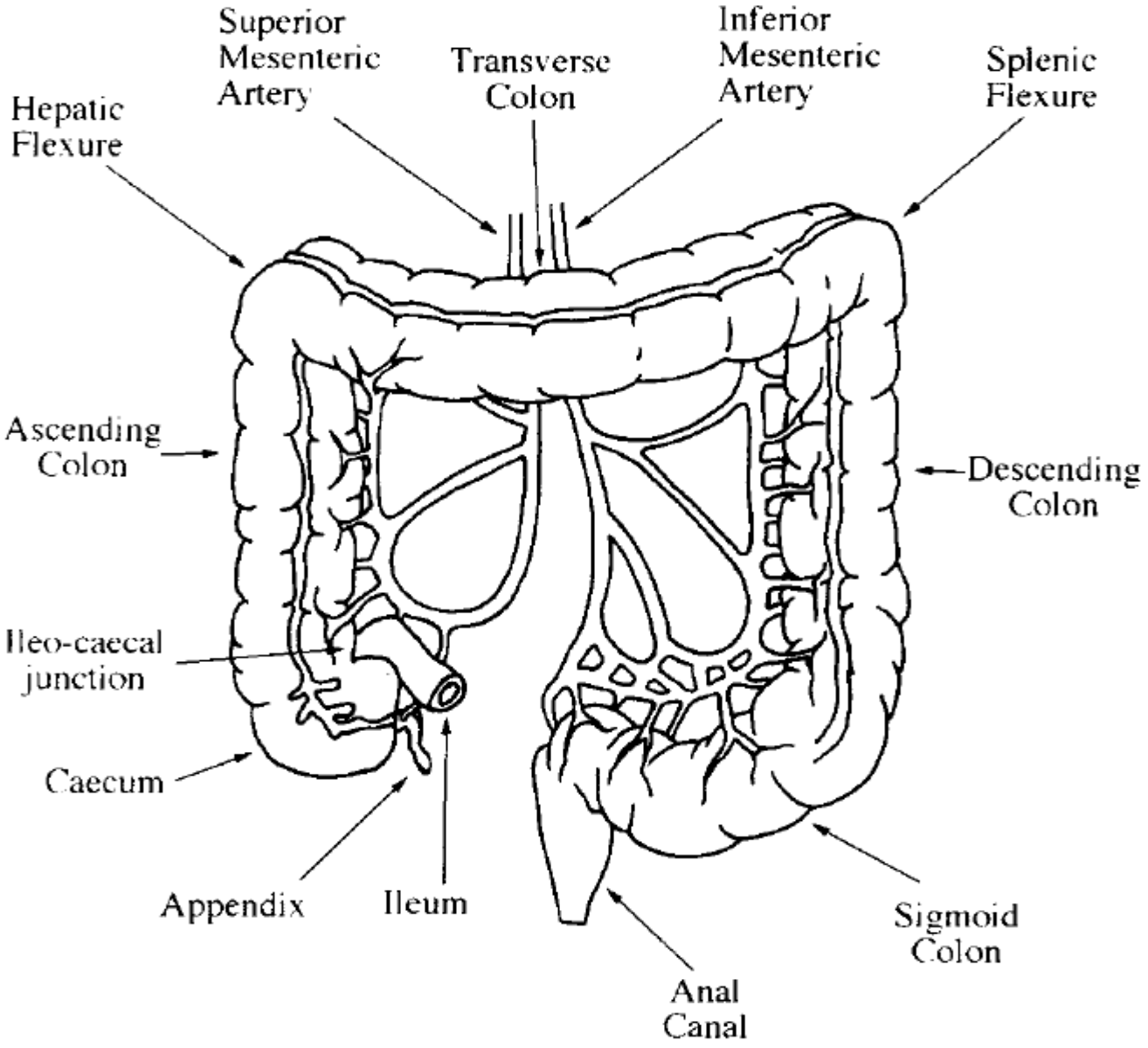


Fig. The Large intestine

Transit of Pharmaceuticals In GIT

Esophageal transit

- This is extremely rapid, usually 10 to 14 seconds.
- Large oval tablets have a shorter esophageal transit than large round tablets.
- Esophageal transit is slower in supine patients than upright ones.

- Tablets/capsules taken in supine position are liable to **lodge** in esophagus especially when taken without water.
    - Capsules, when ingested without water, will remain in the esophagus up to 2 hours without the subject being aware of their presence.
- Recommendation for taking tablets and capsules to avoid esophageal retention is upright, with a sip of water before and then at least 100 ml of water with the medication.

Gastric Transit/Gastric emptying

- Gastric emptying time (GET) is the time that DFs take to traverse stomach.
    - Gastric emptying rate, Gastric residence time.
- The GET is highly variable - ranging between 5 min and 2 hr.
    - It depends on the dosage form type, and fed/fasted state of stomach.

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- Many factors influence gastric emptying

Factors delaying GET

- Fats and fatty acids in diet
- High viscosity of diet
- Lying on left side
- Diseases: Depression, hypothyrodism, gastric ulcer
- Drugs: e.g. propantheline, atropine

Factors promoting GET

- Fasting
- Lying on right side
- Diseases: anxiety, hyperthyrodism
- Drugs: e.g. Metoclopramide

Small Intestinal Transit

- Small intestinal transit time (SITT) is relatively constant, ~ 3 hrs.
- SI does not discriminate b/n solids and liquids, b/n DFs, or b/n fed and fasted states.
- The SITT of dosage forms is not affected by their physical state, size or the presence or absence of food,
    - But, high calorific loads may slow it slightly.

- The SITT is remarkably resistant to pharmaceutical intervention.
- Large amounts of un-absorbable carbohydrate or a large amount of fluid accelerates transit through the small bowel.
    - This could reduce the degree of absorption from a controlled-release formulation taken with the meal.

- Increasing the viscosity of the luminal contents will prolong SITT.
    - This may be important for slowly released or slowly absorbed drugs.

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- SITT is particularly important for:
  - CR, SR, PR DFs (release drug slowly);
  - Enteric-coated DFs (DR) (release drug in SI);
  - Drugs that dissolve slowly in intestinal fluids; and
  - Drugs absorbed by intestinal carrier-mediated transporters.

Colonic Transit

- Long and variable (vary from 2 - 48 hr.).
- Characterized by short bursts of activity followed by long period of stasis.

The GI Environment

Gastric pH

- Gastric pH is primarily influenced by two **factors**; acid secretion and gastric content.

- The average pH is 2.7 in the body and 1.9 in the antrum of the stomach.

    - Due to the differences in the distribution of parietal cells, and the different patterns of motility in various regions of the stomach.

- Food buffers and neutralizes gastric acid, producing an increase in pH.

- A circadian rhythm of basal gastric acidity is known to occur with acid output being highest in the evening and lowest in the morning (??).

- Important considerations for Gastric pH:
  - Chemical stability of the drug
  - Drug dissolution or absorption

Intestinal pH

- The residence of the formulation in the SI has to be long enough for complete absorption to take place.
- Most drugs are absorbed by passive diffusion in their **unionized** state.
- The pH of the SI determines the degree of ionization and hence controls the efficiency of absorption

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- Intestinal pH is higher due to neutralization the gastric content with **HCO_3^-** (bicarbonate ion) secreted by pancreas.

- There is a gradual rise in the intestinal pH along SI.

Location	Fasted state pH	Fed state pH
Duodenum	6.1	5.4
Jejunum	6.6	6.2
Ileum	7.4	7.5

Colonic pH

- pH in the colonic lumen drops to 6.4 - 7.0.
- This due to breakdown of undigested CHOs into short-chain fatty acids.

Luminal enzymes

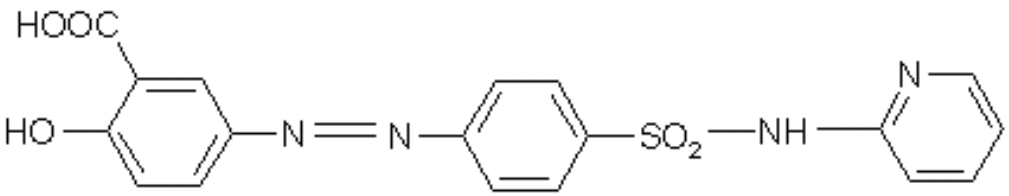
- Pepsin is a primary enzyme in the gastric juice.
    - Pepsinogen is converted to the active enzyme, pepsin, by hydrolysis of the precursor by HCl.
    - The HCl present in the stomach provides the correct pH for the pepsins to act.
- Some other enzymes, including gastric lipase and gastric amylase and gelatinase can be found in gastric juice.
- Lipases, amylases and proteases are secreted from pancreas into SI in response to ingestion of food.

- Pepsins and proteases degrade protein and peptide drugs.
- Drugs resembling nutrients, such as nucleotides and fatty acids, may be susceptible to enzymatic degradation.
- Lipases may affect release from fat/oil-containing DFs.

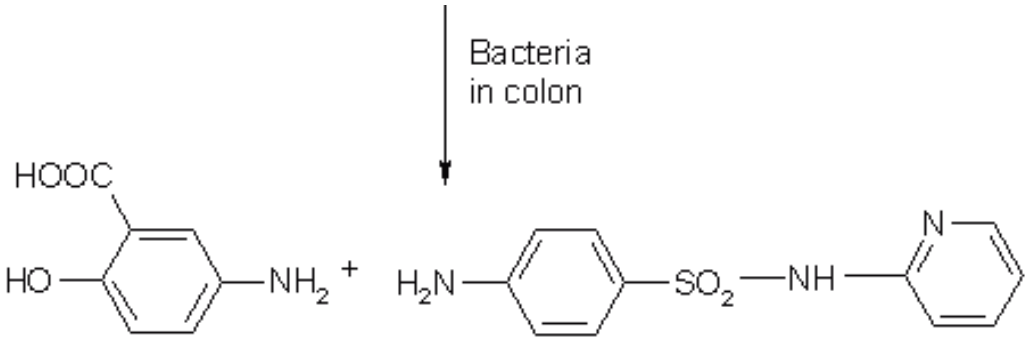
- Colonic bacteria secrete enzymes capable of range of reactions
  - Important for drugs and DFs targeting the colon

  E.g. Prodrug - **Sulphasalazine** (for inflammatory bowel disease) –

  - Sulphasalazine is 5-aminosalicylic acid linked to sulphapyridine via azo bond
  - It is too large and hydrophilic to be absorbed, but bacterial enzymes reduce azo bond to release 5-aminosalicylic acid.



Sulphasalazine



5-aminosalicylic acid

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- Reading assignment –
  - Effect of food on the absorption of drugs.
  - Oral absorption and Hepatic metabolism.
  - Oral absorption and GI blood flow.
  - Double peak phenomena (after oral administration of a single dose of a drug)

Physicochemical Factors affecting Oral Absorption

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- Physicochemical properties of drug candidates are characterized by:
  - Ionization/acidity constant (K_a)
  - Aqueous solubility (S)
  - Partition (P) and distribution (D) coefficients
  - Solid-state characteristics

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- The K_a, S, P, D parameters dictate the absorption characteristics of a dug from solution.
- The interrelationship between these parameters is known as pH-partition theory.
- This theory provides a basic frame work for understanding drug absorption.

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pH partition theory

- This theory is based on the assumption that the GIT is a simple lipid barrier to transport of drugs.
- According to the pH–partition hypothesis:
  - The unionized form of either acids or bases will diffuse across the membrane, while the ionized forms will be rejected.
  - pH dependence of drug absorption and solute transport across membranes is considered.

...

- The Henderson-Hasselbach equation -
  - For weakly acidic drugs:

$$pK_a - pH = \log \frac{[\text{ionised form}]}{[\text{unionised form}]}$$

  - For weakly basic drugs:

$$pH - pK_a = \log \frac{[\text{ionised form}]}{[\text{unionised form}]}$$

...

- From the above equations one can calculate the relative amounts of absorbable and non-absorbable forms of a drug substance.
- The larger the proportion/fraction of the non-ionized form, the faster is the absorption of the drug.
- Acid and neutral drugs may be absorbed from the stomach but basic drugs are not.

...

- However, there are several reasons that the pH–partition hypothesis may not be applied quantitatively in practical situations.

- For example, salicylic acid is absorbed from rat intestine at pH 8, although with a pK_a of 3.0 it is virtually completely ionized at this pH.

...

- There are explanations for deviation from pH partition theory:
  - Absorption and ionization are both dynamic processes and that the small amount of unionized drug absorbed is replenished.
  - The bulk pH is not the actual pH at the membrane.
    - A local pH exists at the membrane surface which differs from the bulk pH.

...

- A large surface area and a relatively longer residence time in the SI.
- Convective water flow - the movement of water molecules into and out of the alimentary canal will affect the rate of passage of small molecules across the membrane.
- Unstirred water layers - a layer of relatively unstirred water lies adjacent to all biological membranes.

...

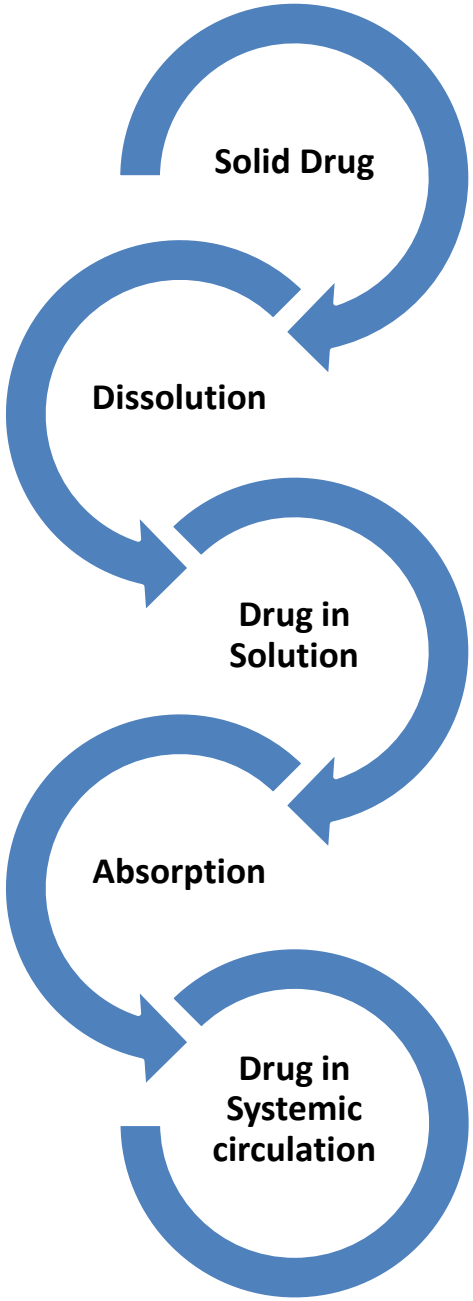
Lipid solubility

- Unionized forms a drug may be poorly absorbed from the SI.
- Compounds with the same pKa may show differences in the extent of their absorption.
- Lipid soluble drugs with favorable partition coefficients are usually well absorbed.
- The structure of an existing drug can be modified to improve absorption.
    - For this, lipid soluble prodrugs are preferred.

...

Effect of dissolution rate

- When a drug is given orally, the rate of absorption is often controlled by how fast the drug dissolves in the fluid at the absorption site.
- When dissolution is the controlling step in the over-all process, absorption is said to be **dissolution rate limited**.
- Dissolution??
- Solubility??


Solid Drug
Dissolution
Drug in Solution
Absorption
Drug in Systemic circulation

...

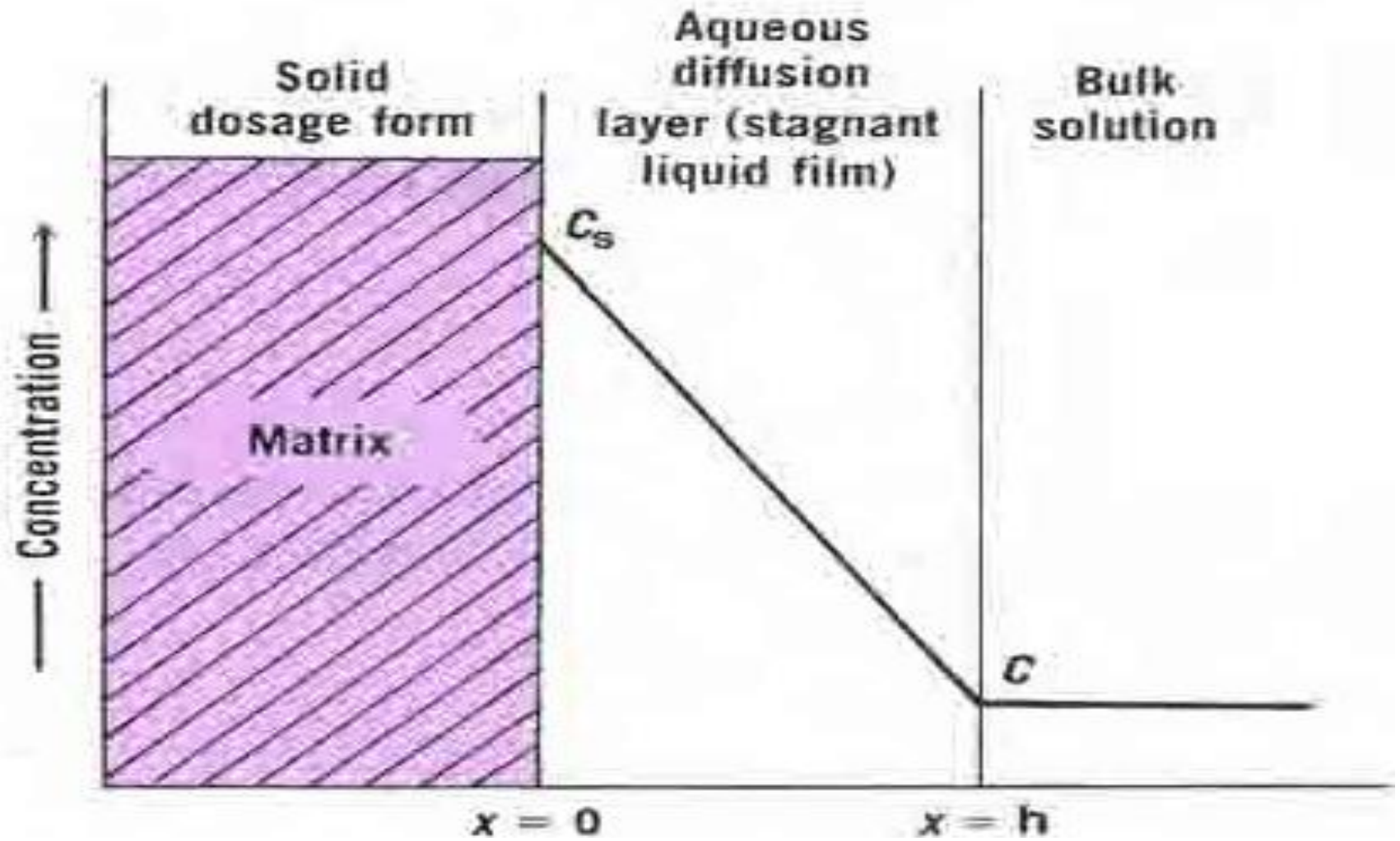
- Dissolution of solid in liquid is composed of two stages:
  - ➢ Interfacial reaction liberates solute molecules from solid phase
    - Involves phase change (molecules of solid become molecules of solute in solvent)
    - Solution in contact with solid will be saturated (concentration will be Cs, saturated solution)

...

- Solute molecules migrate through boundary layers (static layer of liquid surrounding wetted solid surfaces) to bulk of solution.

  - Once solute passes boundary layer, rapid mixing occurs and concentration gradient is destroyed; concentration will be C.

...


Solid dosage form
Aqueous diffusion layer (stagnant liquid film)
Bulk solution
Concentration
C_s
Matrix
C
$x = 0$
$x = h$

...

- Concentration of solution in boundary layer changes from being Cs at crystal surface to bulk concentration C at its outermost limit.
  - Obey Fick's law of diffusion, i.e. Rate ∝ concentration difference between two sides of diffusion layer

$$\frac{dC}{dt} = k\Delta C$$

where

- k is dissolution rate constant
- ΔC is difference in conc. at solid surface (Cs) and bulk (C)

...

- A general relationship describing the dissolution process was first described by Noyes and Whitney.

- The Noyes-Whitney equation:

$$\frac{dC}{dt} = kS(C_s - C)$$

where

- $\frac{\boldsymbol{dC}}{\boldsymbol{dt}}$ is the dissolution rate
- k is dissolution rate constant
- S is SA of dissolving solid
- Cs is concentration at solid surface and C is concentration at bulk

...

- The constant k in the Noyes-Whitney's equation has been shown to be equal to $\frac{\mathbf{D}}{\mathbf{h}}$, where D = diffusion coefficient and h= thickness of the diffusion layer.

$$\frac{dC}{dt} = \frac{DS}{h}(C_s - C)$$

...

- Assumptions:
  - Drug particles are spherical and equal in size,
  - Dissolution process is controlled by diffusion,
  - No chemical reaction between drug and components of fluid,
  - Thickness of diffusion layer (h) and saturation solubility (Cs) are constant irrespective of particle size.

...

- The diffusion layer is like the unstirred water layer in the intestine.
  - It is a stationary film of solution adjacent to the surface of the solid.
  - The concentration of drug in this layer is equal to Cs.
  - If the absorption is dissolution rate-limited, C is negligible compared to Cs in the Noyes-Whitney's equation.

...

- The Noyes-Whitney's equation can be re-written as:

$$\frac{dC}{dt} = \frac{DS}{h}(C_s)$$

- Therefore, dissolution might depend on:
  - Temperature, which affects the solubility (Cs)
  - Viscosity, which affects the diffusion coefficient (D)

...

- The degree of agitation, which affects the thickness of the diffusion layer (h)
- Changes in the solvent that affects the solubility
- The effective SA

...

Dissolution and pH

- The solubility of weak acids and bases can change considerably as a function of pH.
  - Solubility of a weak acid is given by:

$$C_s = [HA] + [A^-]$$

Where, $[HA] = C_o$ and $[A^-] = \frac{k_a C_o}{[H^+]}$ then,

$$C_s = C_o + \frac{k_a C_o}{[H^+]}$$

...

- Similarly, solubility of a weak base is given by:

$$C_s = C_o + \frac{C_o[H^+]}{k_a}$$

...

- Substituting the above equations into the Noyes-Whitney's equation;
  - For a weak acid:

$$\frac{dC}{dt} = K'\left[C_o + \frac{k_a C_o}{[H^+]}\right] \quad \text{Or} \quad \frac{dC}{dt} = K'C_o\left[1 + \frac{k_a}{[H^+]}\right]$$

  - For a weak base:

$$\frac{dC}{dt} = K'C_o\left[1 + \frac{[H^+]}{k_a}\right]$$

...

- From the above equations:
  - The dissolution rate of weak acids increases with increasing pH
  - The dissolution rate of weak bases decreases with increasing pH

...

- Its important for poorly soluble weakly basic drugs to be dissolved rapidly in the stomach.
    - Ketoconazole, a weakly basic drug, requires acidity for dissolution and absorption.
        - Drugs which reduce gastric acidity (like, antacids, anticholinergics, and H_2-blockers) will reduce its absorption.

...

- Changes in the gastric pH alter the solubility of certain drugs and may affect dissolution and absorption.

Dissolution and Diffusion layer pH

- The relationships that have been described between dissolution rate and $[H^+]$ may tend to over predict dissolution rates of weak acids in the SI, and weak bases in the stomach.

...

- The $[H^+]$ in the bulk is not equal to the $[H^+]$ in the diffusion layer.
- In general,
  - $[H^+]_d > [H^+]$, for weak acids
  - $[H^+]_d < [H^+]$, for weak bases

...

Dissolution and Salt forms

- The dissolution rate of a particular salt is usually different from that of the parent compound.
  - Strong base salts of weak acidic drugs dissolve more rapidly than the free acids.
  - Strong acid salts of weak basic drugs dissolve more rapidly than the free bases.

...

- The effect of salt formation on dissolution rate requires a consideration of the pH of the diffusion layer,
  - The pH of the diffusion layer is always greater for strong base salts of weak acids.
  - The pH of the diffusion layer is always smaller for strong acid salts of weak bases.

...

Chemical stability of drugs in the GI fluids

- Hydrolysis of drugs in the GIT is sometimes the reason for poor bioavailability.
    - E.g. Chemical inactivation in the stomach is responsible for the relatively low bioavailability of penicillin G and methicillin.
- When a drug is unstable in the gastric fluids, rapid dissolution may reduce bioavailability (why?).

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- Some **prodrugs** must be hydrolyzed to the parent drug in the GI fluid to produce clinical effect.
    - Failure to achieve complete conversion will result in absorption of the prodrug itself which has little or no clinical effect.
    - Chemical or enzymatic conversion of the prodrug to parent drug in blood or tissues may be limited.
        - The prodrug may be metabolized or excreted unchanged.

...

Solid-state characterization

- During selection of drug candidates, crystal forms are characterized by means of investigating their influence on dissolution.

- Solvation-limited poor-solubility

    - Represent highly lipophilic species that are unable to form bonds with water molecules

...

- Solid-state-limited poor-solubility
  - Represent stable crystals in which the strong intermolecular bonds within the crystal restrict the solubility of the candidate with water.
  - For such kind of drug candidates dissolution may be limiting for bioavailability.
  - Crystal habits may have an influence on dissolution and thus bioavailability.
  - The solid-state properties may significantly influence formulation strategies as well the physical and chemical stability of these candidates.

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Polymorphism

- Polymorphism refers to the arrangement of a drug substance in various crystal forms or polymorphs.
    - Polymorphs have the same chemical structure but different physical properties, such as solubility, density, hardness, and compression characteristics.
    - Some polymorphic crystals have much lower aqueous solubility than the amorphous forms, causing a product to be incompletely absorbed.

...

- Some polymorphs are metastable and may convert to a more stable form over time.
- At given T and P, only one crystalline form is stable and others are metastable
- Metastable tend to transform to most stable form
  - Metastable polymorphs have higher energy and usually lower m.pt., greater solubility and dissolution rates
  - One polymorph may be therapeutically active than another!

...

- E.g. Chloramphenicol palmitate exists in 3 crystalline forms designated A, B and C
  - Polymorph C is too unstable to be included in DFs
  - Polymorph B is sufficiently stable
  - Polymorph A is stable – therapeutically inactive
- Extent of absorption increase in proportion of polymorph B

...

Solvates

- Drugs associated with solvent molecules to produce crystalline forms,
    - When water is solvent, solvate is called **hydrate**!
- Solvated and non-solvated forms usually exhibit differences in dissolution rates.
- Greater solvation of crystal means lower solubility and dissolution rate in solvent identical to solvation molecule.

Formulation Factors affecting Oral Absorption of Drugs

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Effects of excipients

- Excipients are added to a formulation to provide certain functional properties.
- Excipients in the drug product may affect the dissolution kinetics of the drug.
  - By altering the medium in which the drug is dissolving or
  - By reacting with the drug itself

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- Excipients may affect dissolution in different ways:
  - Suspending agents may increase the viscosity of the medium.
  - Tablet lubricants may repel water and create wetting problem.
  - Coatings may crosslink upon aging and decrease the dissolution rate.

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- Surfactants:
  - **Low** concentrations decrease the surface tension and increase the rate of drug dissolution.
  - **Higher** surfactants concentrations tend to form micelles.
- Some excipients may change the pH of the medium.
- Some may interact directly with the drug to form a water-soluble or water-insoluble complex.

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- Excipients may be added intentionally to the formulation to **enhance** or **delay** the rate and extent of drug absorption.

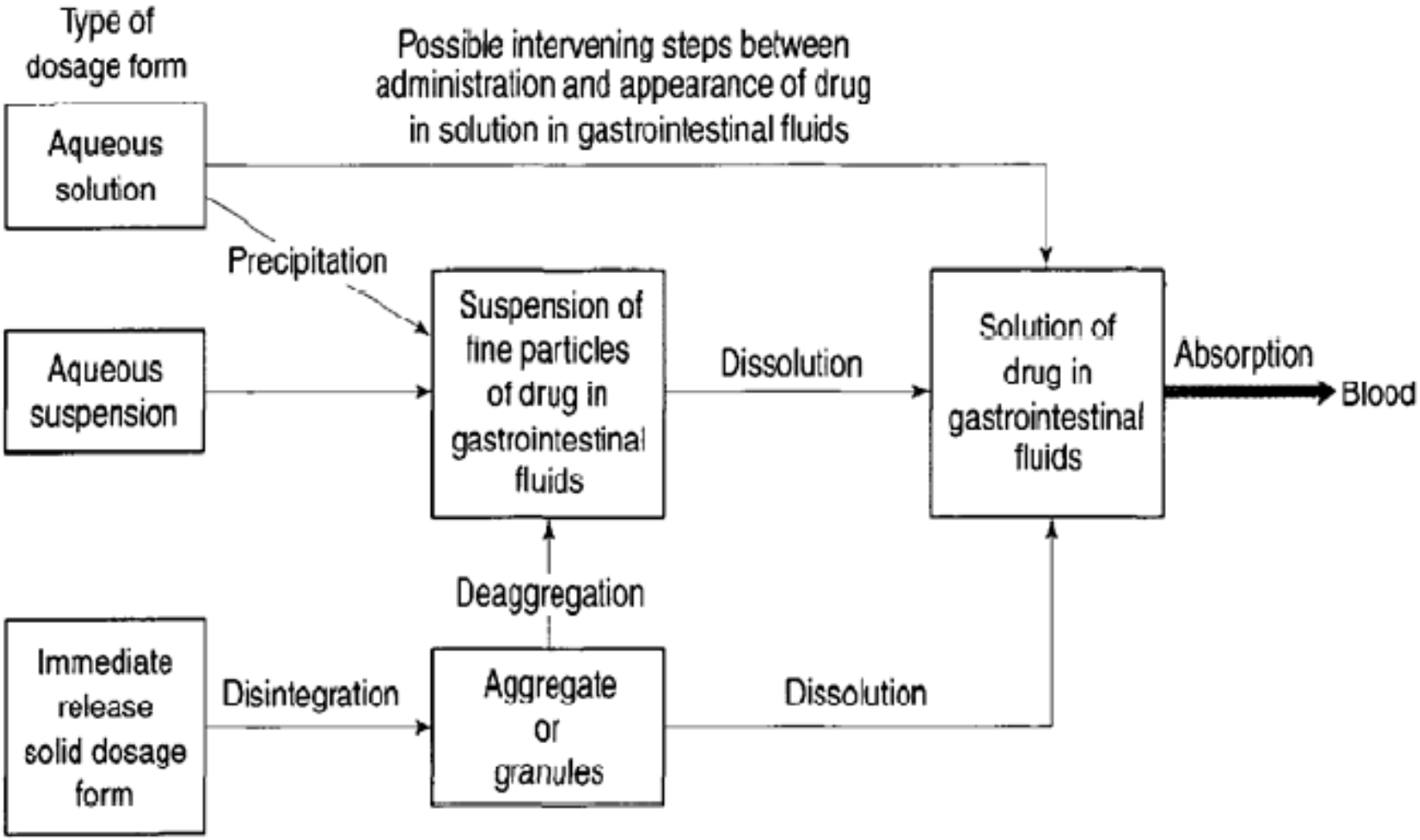
  E.g. Excipients enhancing the rate and extent of drug absorption:

  - Excipients that increase the aqueous solubility of the drug.
  - Excipients increasing the retention time of the drug in the GIT.
  - Excipients acting as carriers to increase drug diffusion across the intestinal wall.

...

Effects of dosage form type

- Type of DF and its method of preparation or manufacture influence bioavailability.
- Type of DF influence number of possible intervening steps between administration and appearance of dissolved drug in GI fluids.
    - Greater number of intervening steps means greater number of potential obstacles to absorption and greater likelihood of DF to reduce bioavailability.


Type of dosage form
Possible intervening steps between administration and appearance of drug in solution in gastrointestinal fluids
Aqueous solution
Precipitation
Aqueous suspension
Suspension of fine particles of drug in gastrointestinal fluids
Dissolution
Solution of drug in gastrointestinal fluids
Absorption
Blood
Deaggregation
Immediate release solid dosage form
Disintegration
Aggregate or granules
Dissolution

...

- Read

1. Effect of soluble salt formation on the dissolution and absorption, and clinical response of different drug.

2. Effect of prodrug formation on the dissolution and absorption, and clinical response of different drugs.

3. Effect of SA and particle size on the dissolution and absorption, and clinical response of different drugs.

4. Effect of Complexation and adsorption on the dissolution and absorption, and clinical response of different drugs.

...

5. Aqueous solutions and suspensions and factors influencing oral bioavailability from these DFs.

6. Liquid-filled and Powder-filled capsules and factors influencing oral bioavailability from these DFs.

7. Tablets and factors influencing oral bioavailability from these DFs.